



**Background Paper on Vaccination against Typhoid Fever using New-
Generation Vaccines - presented at the SAGE November 2007 meeting**

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Executive Summary

Introduction

Typhoid fever, caused by the bacterium, *Salmonella enterica* serovar Typhi (*S. Typhi*) remains an important cause of enteric disease in children in developing countries. The disease results in an estimated 216,000 – 600,000 deaths per year, predominantly in children of school-age or younger, making it comparable in mortality to several other priority vaccine-preventable diseases, including rotavirus and HPV. An estimated ninety percent of deaths occur in Asia.

The disease is transmitted through the faecal-oral route and is most common in areas with poor water and sanitation systems and practices. Antibiotic resistant strains of the disease, including multi-drug resistant strains, have spread to many areas, reducing the effectiveness of common antibiotics and increasing the urgency to control the disease. While largely an endemic disease, outbreaks of typhoid occur periodically, including outbreaks of antibiotic resistant strains.

Two new-generation typhoid vaccines have replaced the old, reactogenic inactivated whole-cell vaccines used in the past. These new-generation vaccines – live oral Ty21a and injectable Vi polysaccharide – have been shown in large-scale clinical trials to be safe and moderately efficacious and are internationally licensed for persons two years and older. The single-dose injectable Vi vaccine provides around 70% protection, and protection lasts at least three years. The liquid formulation of Ty21a – the formulation most likely to be used in developing countries – is given in 3-4 doses, each spaced two days apart and provides 53-78% protection, and protection has been documented for at least five years. Herd protection of non-vaccinated persons has been documented for Ty21a, but has yet to be evaluated for Vi.

The continued burden of typhoid fever and the alarming spread of antibiotic resistant strains led the WHO in 1999 to recommend immunization using these new-generation vaccines in school-aged children in areas where typhoid fever poses a significant problem and where antibiotic resistant strains are prevalent. However, with the exception of certain provinces in China, parts of Vietnam and one state in India, this recommendation has yet to be implemented in typhoid-endemic countries.

New data from Asia on the disease and economic burden of typhoid fever, recent trends in antibiotic resistance, and vaccine effectiveness and cost-effectiveness, along with the increased availability of typhoid vaccines and sharp reductions in their price, call for WHO to update and reinforce its recommendations for the use of typhoid vaccines for populations at high risk, so that this disease can truly be controlled in countries where it remains a significant public health problem.

New Findings

Among the new findings from field studies conducted by the Bill and Melinda Gates Foundation-funded *Diseases of the Most Impoverished (DOMI)* Programme and from the programmatic use of typhoid vaccines in China, are the following:

- Children in poor urban areas in Asia remain at high risk of getting typhoid fever. Prospective disease burden studies in five Asian study sites found annual incidence rates of blood culture-confirmed typhoid fever of 180-494/100,000 among 5-15 year olds¹ in three urban slum areas (North Jakarta, Indonesia; Kolkata, India and Karachi, Pakistan). Rates of more than 100/100,000 are considered high. Given the approximate 50% sensitivity of blood cultures in detecting *S. Typhi*, actual incidence rates in these sites are likely to be twice as high as the blood-culture proven rates.
- While these studies confirm that school-aged children are at particularly high risk, pre-school children as young as two years old were shown to also be highly vulnerable. Children less than five years old had blood culture-proven disease rates of 573/100,000 in Karachi (the highest of any age group), 340/100,000 in Kolkata, and 149/100,000 in North Jakarta.
- Hospitalization rates of 20-40% among culture-confirmed typhoid cases were found in the study sites in North Jakarta; Hue, Vietnam and Hechi, China, indicating that the disease can be severe in a significant portion of patients.

¹ School aged children considered as those between 5-15 years of age; pre-school children considered 2-4 years of age; and young adults reflect 16-19 year olds

- Antibiotic strains continue to increase and spread in many parts of Asia, reducing the effective treatment options for the disease, increasing treatment costs and increasing the risk of complications and death. Two-thirds of all isolates tested in Karachi, Pakistan were multi-drug resistant (MDR). Nearly 60% of those tested in Kolkata and Karachi and 44% of those in Hue, Vietnam were resistant to naladixic acid – making these cases less responsive to ciprofloxacin and other fluoroquinolones that are often used in areas where MDR typhoid is prevalent. One hundred percent of strains tested in the Mekong Delta of Vietnam have now been found to be naladixic acid resistant.
- Typhoid incidence varies considerably within countries, underscoring the fact that typhoid control, including vaccination, can focus on high-risk populations, instead of being universally applied within countries.
- The average cost of typhoid illness across six Asian study sites was \$15-182 for all cases, but was \$129-\$810 for hospitalized cases. The majority of costs were borne by families, a significant portion of whom had to borrow money to pay for these costs.
- Socio-behavioral and private demand household surveys conducted in the DOMI study sites found that typhoid fever is well recognized as a distinct disease entity in high-risk populations and perceived as a serious problem. The studies indicate considerable population demand for effective typhoid vaccines in these low-income populations.
- A cost-effectiveness analysis of Vi typhoid vaccination of high risk populations, based on country-specific field data on age-specific incidence, cost-of-illness, population demand for typhoid vaccines, and cost of Vi vaccination from the DOMI studies, found vaccination of school-aged² and pre-school children³ to be "very cost effective" in the high incidence slums of Kolkata, Karachi and North Jakarta (cost per DALY averted of \$177-\$674), using the WHO definition and considering only the costs of the illness borne

² School-aged children defined as 5-15 year olds

³ Pre-school children defined as 2-4 year olds

by the public sector. Immunization programmes that included adults as well as children were found to be "very cost-effective" in Kolkata and North Jakarta⁴.

- Demonstration projects using Vi vaccine and Ty21a have shown large-scale community- and school-based vaccination to be feasible and well accepted by populations in endemic countries.
- Evidence from China suggests that the programmatic use of Vi vaccine in selected areas largely controlled the disease within a four to five year period, reducing incidence to very low levels. Experience in China also has shown that Vi vaccination is equally effective in controlling currently-occurring typhoid outbreaks as in reducing endemic disease.

Although large outbreaks of typhoid fever have been reported from other regions, including Africa and Central Asia, there is limited data on the population-based incidence rates or burden of typhoid fever from these regions. This is compounded by reports that non-typhi salmonella are common in parts of Africa. Finally, the global spread of antibiotic resistant strains in Africa and Central Asia is well documented implying the need for continued studies and surveillance in these regions.

Vaccine Supply and Prices

The number of producers of Vi vaccine has increased significantly in the past several years, including several producers in India, China and Cuba. Two vaccine manufacturers in India and Indonesia should have locally licensed Vi vaccines on the market in the next two to three years. There are now two producers of Ty21a, one in Switzerland and the other in South Korea. Neither vaccine is patent-protected, opening up the possibility of additional producers in the future.

At least six Vi producers and the two Ty21a producers have the potential to have their vaccines pre-qualified by WHO – a requirement for its purchase by UN agencies and the GAVI Alliance. The increase in the number of producers has increased production capacity, as well as

⁴ The analysis for adult vaccination was not performed for Karachi, since prospective disease surveillance conducted by DOMI did not include adults

significantly reduced vaccine prices. One large-scale Vi producer alone can manufacture 100 million doses per year. Current production capacity can therefore easily meet the increased demand for typhoid vaccines, if they are introduced into high-risk areas of endemic countries.

Recognized developing country vaccine producers have quoted prices of Vi polysaccharide vaccine to public health programmes in developing countries of ~\$0.50 or less in multi-dose vial presentations, and the main producer of Ty21a is also offering tiered prices. There is the potential for vaccine prices to fall further with increased demand and with more producers entering the market.

Typhoid Vaccines in Development

Both Vi conjugate vaccines – designed to be effective in infants – and new oral live vaccines – designed to be highly immunogenic in a single dose – are currently in development. A prototype Vi conjugate vaccine was found to be highly efficacious (89%) in Vietnamese toddlers and pre-school children during 46 months of follow-up (including 91% efficacy during 27 months of active surveillance and 82% efficacy during 19 additional months of passive surveillance). Serum antibody responses in the vaccinated Vietnamese children suggest that the conjugate vaccine may be able to protect for at least 10 years in persons five years and older.

Several groups are now developing Vi-diphtheria toxoid (DT) conjugate vaccines, with the goal of transferring technology to appropriate developing country producers, so that low-cost typhoid conjugate vaccines can ultimately be potentially incorporated into the infant EPI schedule for high-risk populations. It is hypothesized that immunization of infants with conjugate vaccine will result in protection that endures through the pre-school and early school-age years. It will be important to document this.

A number of improved live oral vaccines are currently in clinical trials. However, all of these newer generation typhoid vaccines are still several years away from being licensed and available on the market. The future promise of these vaccines should not preclude the more immediate use of currently available new-generation vaccines in endemic populations.

Proposed Recommendations

1. In view of the continued high incidence of typhoid fever and increasing antibiotic resistance, and given the safety, efficacy, feasibility and affordability of two licensed vaccines (Vi and Ty21a), countries should consider the programmatic use of typhoid vaccines for controlling endemic disease;
2. In most countries, the control of the disease will require only vaccination targeted to high-risk groups and populations, as opposed to universal vaccination;
3. The selection of populations and age groups to target and the delivery strategy (school- or community-based vaccination) should be up to specific countries and will depend on the local context (*eg.* age pattern of the disease, school enrolment rates, *etc.*);
4. The selection of typhoid vaccine – Ty21a and Vi – should be made by the countries themselves, and depend on the capacity of the local EPI programme and other logistic and cultural factors, and utilizing opportunities coupled to other public health interventions in these specific age groups;
5. The availability of licensed typhoid vaccines for the poor will be enhanced by the pre-qualification by WHO of these products and by the enhanced global awareness and commitment to reduce typhoid disease burden;
6. Due to the epidemic potential of typhoid, and past observations in the effectiveness of vaccination in interrupting outbreaks, typhoid vaccination is recommended for outbreak control;
7. All typhoid vaccination programmes should be implemented in the context of other efforts to control the disease, including health education, water quality and sanitation improvements, and training of health professionals in diagnosis and treatment;

8. Given the importance of information on disease incidence for targeting vaccination and assessing impact, priority should be given to strengthening surveillance systems for typhoid fever, including sentinel site surveillance in pre-school (2-4 year olds) and school-aged children (5-15 year olds). The development of reliable and appropriate diagnostics assays for developing countries is required;

9. Development and research of new typhoid vaccines (such as the Vi conjugate vaccine) are encouraged for use in infants and young children, but this should not limit the implementation of the current available vaccines for control of endemic disease.

I. Introduction

Key points

- Typhoid fever is a disease transmitted by the faecal-oral route that continues to be a public health problem in many developing countries, with children disproportionately affected.
- Improvements in water and sanitation systems and hygiene education are effective methods to control typhoid fever, but are slow to be implemented in many typhoid-endemic countries.
- Two new-generation vaccines (Vi and Ty21a) have been shown to be safe and effective and have been licensed for persons two years and older in many countries.
- WHO recommended use of these new vaccines in 1999 for school-aged children in areas with high incidence and/or antibiotic resistance, but this recommendation has been implemented in very few typhoid–endemic countries to date.
- New data since the 1999 WHO recommendations on the persisting disease and economic burden, increasing antibiotic resistance and the effectiveness of new-generation vaccines in real life situations underscores the need to strengthen the current WHO recommendations.
- Since 1999, the production capacity of these vaccines has increased greatly and prices have dropped to low levels.
- In view of the new data and recent developments in the vaccine landscape, a strong unambiguous position by WHO is required for the use of typhoid vaccines for populations at high risk for typhoid fever and typhoid mortality.

Typhoid fever, caused by the bacterium, *Salmonella enterica* serovar Typhi (often referred to as *S. Typhi*) has become rare in industrialized countries, yet it remains an important cause of enteric disease in children in developing countries, resulting in an estimated 216,000 – 600,000 deaths per year, predominantly in children of school-age or younger [1,2].

As humans are the only source of infection, and transmission of *S. Typhi* is by the faecal-oral route through contaminated water or food, prevention measures need to include water and sanitation improvements, as well as health education. Typhoid fever can be effectively treated with antibiotics, but growing rates of antibiotic resistance in many regions are making this treatment option increasingly more difficult and costly. Given these facts, it seems necessary to consider a comprehensive approach to prevention of this disease that combines targeted vaccination of high-risk populations as a short- to medium-term measure, combined with the longer term solutions of water and sanitation improvements and elevated living standards.

Two new-generation typhoid vaccines have been available on the market since the late 1980s or early 1990s and found to be extremely safe and moderately efficacious. The oral live attenuated Ty21a, currently produced by Crucell⁵ and Boryung in South Korea confers 33-96% protection – depending on the formulation and location where tested – after 3-4 closely-spaced doses, for five to seven years [3] and is licensed for use in persons two years and above (for the liquid formulation) and five years and older (for the capsule formulation). The injectable Vi polysaccharide vaccine, developed by the U.S. National Institutes of Health, is given in a single-dose and was found to confer 64-72% protection for 17-21 months and 55% over three years [4]. Like other polysaccharide vaccines, Vi is not immunogenic in children less than two years of age, and thus is licensed for use in persons two years and above.

The development of these new vaccines, together with the emergence of *S. Typhi* antibiotic-resistant strains and the continued high burden of the disease, led the WHO Department of Immunizations, Vaccines and Biologicals (IVB) in 1999 to recommend immunization using the new-generation typhoid vaccines in school-aged children and young adults “*in areas where typhoid fever in these age groups is a significant problem and particularly where antibiotic resistant S. Typhi strains are prevalent... until socio-economic improvements finally interrupt transmission of S. Typhi*”. These recommendations were published in “Strategies, policies and practices for immunization of adolescents: a review” [5] and then in the WHO Position Paper on Typhoid Vaccines published in the *Weekly Epidemiological Record* in 2000 [1].

⁵ Crucell Holland B.V. has recently acquired Berna Biotech (formerly Swiss Serum and Vaccine Institute)

Unfortunately, the use of new-generation typhoid vaccines by the public sector has thus far been limited to only three countries and only on a limited basis:

- Several provinces and districts in China began mass vaccination campaigns for school children and food handlers in the mid-1990s, using locally-produced Vi. These programmes has been effective in dramatically reducing typhoid incidence in Southwest China (e.g. parts of Guangxi Province).
- The Vietnam National Immunization Programme also began annual campaigns in 1997, using at first imported and later locally-produced Vi for 3-10 year old children in a limited number of high-risk districts. However, Vietnam's programme is considered too limited to effectively control the disease throughout the country.
- Finally in 2004, Delhi State, India introduced Vi vaccination in 2-5 year olds through community-based campaigns⁶.

Many reasons have been given for this lack of uptake of typhoid vaccination in endemic countries, including those gleaned from a survey of policymakers in Asia conducted in 2000-2001 [6]. These include:

- uncertainty of the true typhoid disease burden in most developing countries due to the lack of inexpensive rapid diagnostic tools, infrequency of laboratory testing, poor disease reporting systems and the fact that the clinical diagnosis of the disease is often confused with other febrile illnesses;
- a sense of complacency created by the successful use of relatively inexpensive antibiotics, which substantially reduced typhoid-related deaths, but which have progressively become ineffective due to the acquisition of antibiotic resistance by the bacterium;
- lack of public's attention, as typhoid exacts its toll of morbidity and mortality as an endemic illness;
- political pressure for local government officials not to report "typhoid" cases, since they are considered an indicator of inadequate or failing water and sanitation systems;
- the relatively high prices of the vaccines on the world market, although this situation is now changing, (see below);

⁶ Little information on the immunization coverage and impact of this programme on typhoid incidence is currently available.

- a preference among policymakers for water and sanitation improvements over vaccination to control many enteric diseases;
- a lack of awareness among many policymakers about the new-generation vaccines;
- uncertainty of the logistic feasibility of mass vaccination of children outside of the infant EPI schedule in their countries;

New data and developments since 2000 address many of the issues outlined above and call for WHO to revisit and strengthen its recommendations for the use of typhoid fever vaccines. Field studies have provided new data on the magnitude of typhoid disease, especially in Asia, including incidence rates, age distribution patterns and trends in antibiotic resistance of *S. Typhi*, as well as on the economic burden of the disease. Large vaccine demonstration studies in typhoid-endemic countries of Asia have yielded data on the effectiveness of Vi vaccine; the feasibility, acceptability and costs of large-scale community- or school-based vaccination; and the population demand for new-generation typhoid vaccines. Similar studies with Ty21a in Latin America over a decade ago, also demonstrated the effectiveness, feasibility and acceptability of this vaccine for school based vaccination.

The production capacity, supply and prices of new-generation typhoid vaccines have also changed considerably in the last several years. Besides the international pharmaceutical producers, GlaxoSmithkline Biologicals and Sanofi Pasteur, there is a growing number of high-quality manufacturers in developing countries (“emerging producers”) that produce Vi vaccines. At the same time, Crucell, the producer of Ty21a, has also expressed its willingness to increase production and offer competitive tiered prices to the public sector if there is an increased demand for this vaccine. These developments have greatly increased the feasibility and affordability of broader adoption of typhoid vaccination in high-risk areas of endemic countries.

The most recent in a series of international meetings on typhoid fever and vaccines was organized by the Merieux Foundation and the International Vaccine Institute (IVI) on “*Typhoid fever, a neglected disease: towards a vaccine introduction policy*”, in April 2007. This meeting recommended the broader use of new-generation typhoid vaccines in high-risk areas of endemic

countries and more extensive advocacy to place the use of typhoid fever vaccination higher on the international public health agenda.

As a first step, participants in these meetings considered a review of recent field data and developments in the supply and access of typhoid vaccines by the WHO Strategic Advisory Group of Experts (SAGE) critical, so that revised and strengthened recommendations on typhoid vaccination based on this new information could be issued.

This document provides an update on new developments and data in the field of typhoid fever and typhoid vaccination and provides points of consideration for updated recommendations for review by the SAGE members.

II. The magnitude of the problem of typhoid fever

A. Background on the Disease, Routes of Transmission, Risk Factors and Diagnosis

Key points:

- Typhoid fever is spread by contaminated water and food, especially in areas with poor water and sanitation systems.
- The disease can be severe – with serious complication rates of up to 10% and case fatality rates of 1-4% (vs. 10-20% in the pre-antibiotic era).
- Multi-drug resistance is increasing and spreading globally, reducing effective treatment options for the disease, increasing treatment costs and raising the spectre of higher case fatality rates.
- Global estimates of typhoid disease morbidity and mortality per year are comparable to several other priority vaccine-preventable diseases
- Although largely an endemic disease, typhoid has epidemic potential with major outbreaks reported throughout the developing world (including outbreaks with antibiotic-resistant strains).
- Prospective population-based studies have recently documented high typhoid incidence rates in several parts of Asia, especially in urban slum areas.
- School-aged children are particularly at high risk, and in highly endemic areas, toddlers and pre-school children are at comparably high risk.
- The costs of typhoid illness have been shown to be high, especially for hospitalized cases, with the bulk of costs borne by the family.

Typhoid fever is the most common cause of enteric fever, which also includes paratyphoid fever (caused by *S. paratyphi* A or B). It is a systemic infection caused by *Salmonella enterica* serovar Typhi (*S. Typhi*), a highly virulent and invasive pathogen that affects only humans. The disease is transmitted by the ingestion of food or water contaminated by excreta of patients and asymptomatic carriers and is therefore most common in areas with poor water and sanitation systems and practices. Common sources include polluted water and contaminated food (e.g. milk

products), often eaten outside of the home and handled by infected persons (chronic or transient carriers) [7,8]. Other risk factors for increased transmission include recent typhoid fever in the household, a lack of toilets in the household, drinking unboiled water, not using soap for hand washing, and sharing food from the same plates as others [9-12].

While symptoms can vary broadly in severity, the disease is characterized by the sudden onset of prolonged fever, severe headache, malaise and abdominal pain. The illness often causes diarrhoea, especially in younger children, whereas constipation is common in older children and adults. Serious complications occur in up to 10% of typhoid patients, especially in those who have been ill longer than two weeks and have not received proper treatment [13]. The most common complications include: gastrointestinal bleeding, intestinal perforation (in up to 3% of hospitalized cases) [13], neuropsychiatric disturbances (such as stupor⁷ and delirium), and shock. The illness often lasts several weeks and occasionally even months; the average duration of fever in a study of rapidly identified and appropriately treated culture-confirmed typhoid cases in Delhi, India was 14 days [14].

Current estimates of case fatality of the disease range from 1-4%, including treated patients [1,2,15]. Left untreated, case fatality can climb to 10-20% [3,16]. An estimated 1-5% of survivors, depending on age and gender, become long-term gallbladder carriers of the infection. Chronic biliary carriers have an elevated risk of hepatobiliary cancers [13,17, 18].

Hospitalization rates of typhoid fever cases vary from 10-40%, while the rest either self-medicate or are treated on an outpatient basis [17]. Population-based surveillance studies in five Asian countries conducted by the DOMI Programme, confirmed high rates of hospitalization among blood culture-confirmed typhoid fever cases - from 40% in Hechi, China, to 20% in North Jakarta, Indonesia and 2% in India. The average length of hospital stay in the study was nearly 15 days in China and 9 days in India.

⁷ The term “typhoid” means stuporlike.

Studies from South Asia indicate that typhoid fever can be especially severe in very young children. Children four years or younger had a case fatality rate ten times higher than older children (4.0% vs. 0.4%) [19].

The often non-specific symptoms of typhoid fever can make its clinical diagnosis difficult and it can be confused with malaria, dengue fever, influenza and other febrile illnesses. Confirmed diagnosis requires isolating *S. Typhi* in the laboratory through blood cultures or occasionally through bone marrow culture. Unfortunately, such tests are not conducted for the majority of patients in developing countries, especially those treated in non-hospital settings. The latter has been shown to be approximately 50% more sensitive than blood culture [7, 20-23]. The reliance on clinical diagnosis not only leads to poor surveillance and a considerable underestimation of the incidence of typhoid fever, but also can result in misdiagnosis and inappropriate treatment.

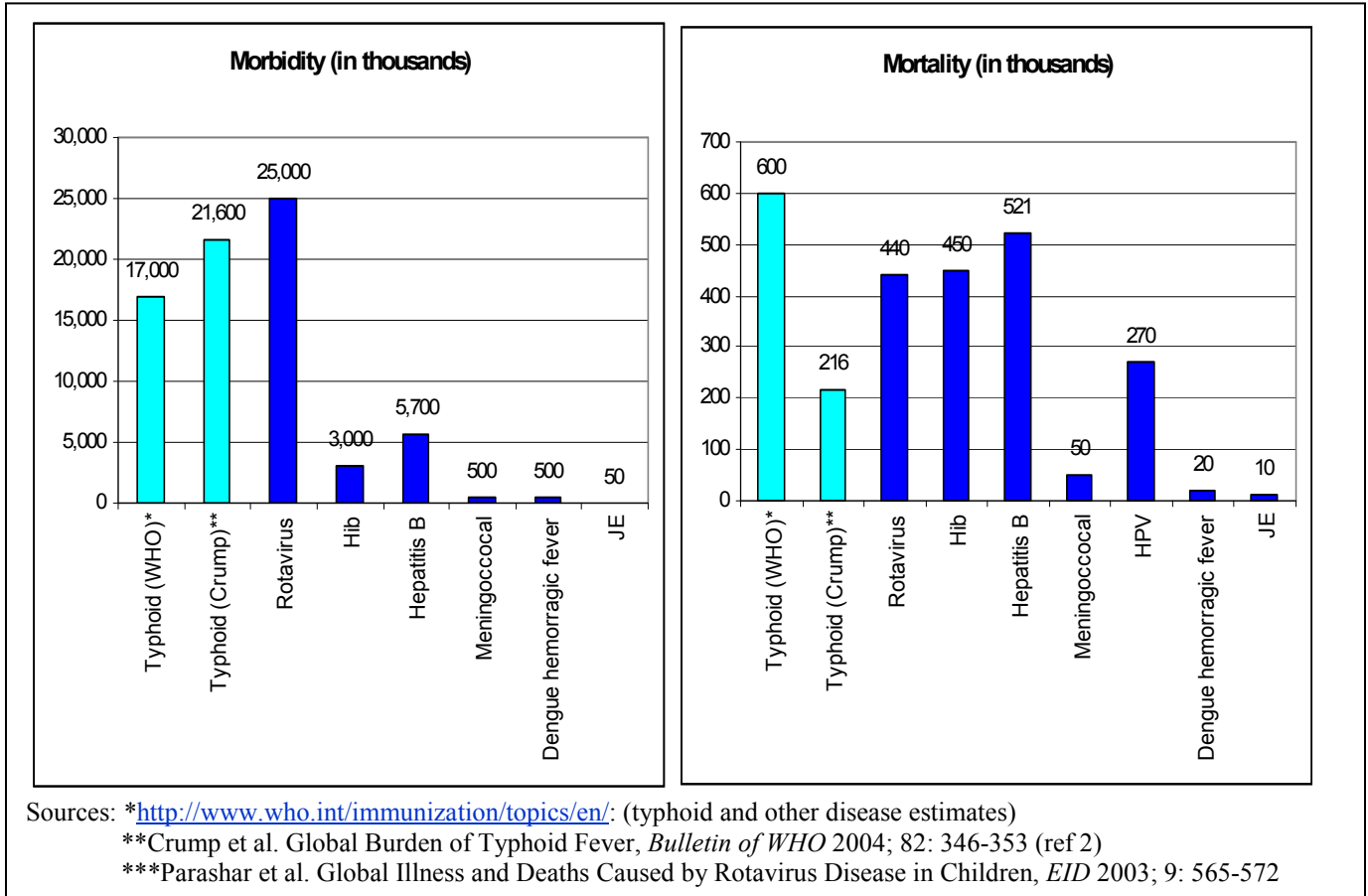
Administration of antibiotics is the preferred treatment option against typhoid fever. However, multi-drug resistant *S. Typhi* has spread to many parts of the world, limiting the ability to treat typhoid fever with commonly-available antibiotics, increasing the costs of treatment (see below), and raising the spectre of higher case fatality rates.

B. Epidemiological Patterns of Typhoid Fever and Implications for Control Programs

B.1. The global burden of typhoid fever

The WHO estimate of the global typhoid disease burden, based on a study from 1984, is around 17 million cases and approximately 500,000 – 600,000 deaths per year [1,13]. This places typhoid fever amongst the high end of diseases for which there are existing under-utilized or new vaccines (see Figure 1). A more recent analysis estimated a similar number of cases per year (21 million) as the earlier estimate, but a lower number of annual deaths (216,000) using the conservative CFR of only 1% [2]. An estimated 90% of typhoid-related deaths occur in Asia [2].

Figure 1. Global Disease Burden Estimates of Typhoid Fever and Other Selected Vaccine-Preventable Diseases



While these recent estimates still represent a high disease burden, precise estimates of the global burden of typhoid morbidity and mortality and its regional distribution are uncertain. Indeed, the recent analysis [2] was based on data from selected studies in a total of only 10 developing countries – and only one in Sub-Saharan Africa (South Africa). High incidence rates of typhoid have been documented for South and Southeast Asia, but arbitrary estimates had to be made for the many regions of the developing world that lacked any data, especially Africa. The paucity of reliable incidence data from most developing countries reflects the fact that laboratories capable of bacteriologic confirmation are lacking in much of the developing world.

Although typhoid fever is largely considered an endemic disease, epidemics do occur frequently, often as a result of contamination or breakdown in water supplies and sanitation systems. In

Tajikistan, for instance, recurrent outbreaks of multidrug resistant (MDR) typhoid that evolved into the first reported epidemic of ciprofloxacin-resistant typhoid caused more than 24,000 cases and a case fatality rate of around 1% from 1996 to 1998 [24]. Over a four-month period in 2004/05, the Democratic Republic of the Congo reported to WHO more than 42,500 cases of typhoid, including 697 intestinal perforations and 214 deaths [25].

B.2. Country-specific incidence rates and high-risk age groups from field studies

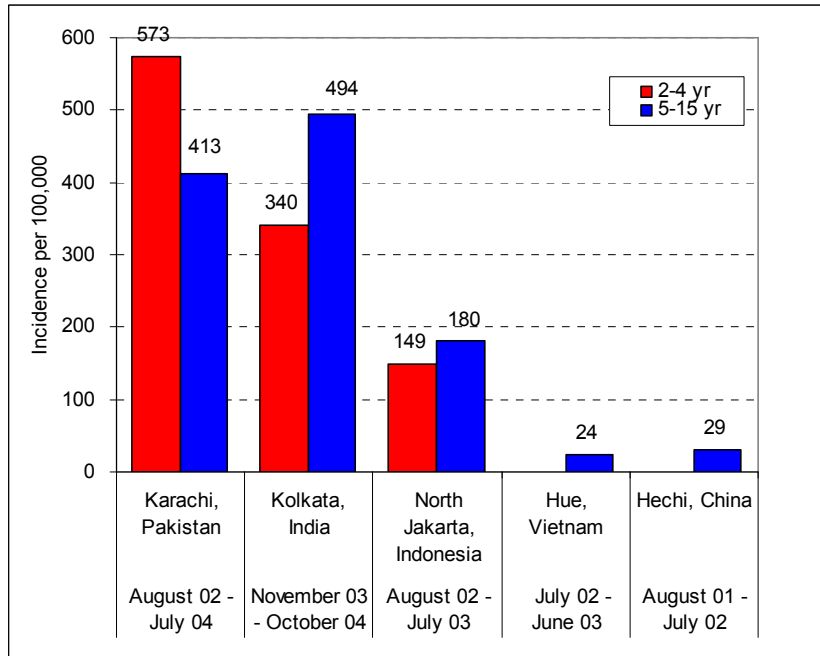
Prospective disease surveillance studies conducted in the 1980s revealed annual typhoid incidence rates in the general population of 100 - 230 per 100,000 in study sites in Santiago, Chile, 440/100,000 in South Africa and 650 and 810/100,000 in study sites in Nepal and Indonesia, respectively [7]. Twenty years later, prospective population-based surveillance studies conducted by the DOMI Programme in five Asian sites (North Jakarta, Indonesia; Karachi, Pakistan; Hechi, China; Hue, Vietnam and Kolkata, India), have revealed that impoverished populations in many locations, especially in urban slum areas, still suffer high rates of the disease (defined as >100/100,000 by Crump *et. al.* [2]. Annual incidence rates of blood-culture confirmed typhoid fever among 5-15 year olds are illustrated in Figure 2. Assuming that blood cultures are only 50% sensitive for detecting typhoid [7,20-23], the actual incidence rates among 5-15 year olds may be double these figures.

In the three sites where pre-school children⁸ were included in the surveillance – Karachi, Kolkata and North Jakarta – the incidence rates for these children were found to quite high (Figure 2). This growing body of evidence suggests that typhoid is not only a disease of school-aged children⁹, but that toddlers and pre-school young children are also at high risk of typhoid fever or typhoid bacteraemia. In several highly-endemic areas in Asia, it appears that the higher the overall incidence, the greater the proportion of invasive *Salmonella* Typhi infection among toddlers and pre-school children.

⁸ Defined as children 2-4 years of age

⁹ Defined as children between 5-15 years of age

Figure 2. Annualized Rates of Blood Culture Confirmed Typhoid Fever in Five Asian Study Sites in the DOMI Programme



Note: Children under five years of age were not included in the surveillance in Vietnam and China sites

Source: Diseases of the Most Impoverished Programme

Therefore, controlling typhoid in highly-endemic areas, particularly in South Asian countries, may well require vaccination of pre-school, as well as school-aged children, at least until a vaccine that can be included in the infant EPI schedule becomes available.

Studies on the incidence and burden of disease of typhoid in Africa are relatively sparse, in large part because of the limited availability of clinical bacteriology laboratories to perform blood cultures. Nevertheless, data exist from a few population-based surveys and systematic hospital-based studies carried out in Africa. A recent report from Egypt indicated a population based incidence of 59/100,000 person years [26], and typhoid has been described as a major health problem in school children in Rwanda and Kenya [27], and is concentrated in peri-urban slums in Kenya [S. Karuiki, personal communication]. In addition, multidrug resistant strains of *S. Typhi* are increasing in incidence in Africa with 75-82% multidrug resistant strains reported in Kenya [28].

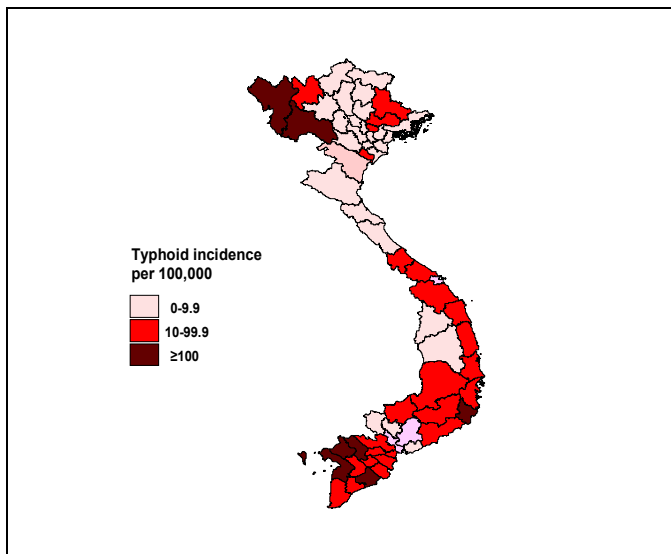
Similarly, typhoid has been reported in large epidemics from central Asia, implying a large public health burden, although the population based incidence rates have not been investigated [24].

B.3. Intra-country variations

The incidence of typhoid fever may vary considerably not only between, but also within, countries. A meta-analysis of incidence data in Vietnam showed that 90% of typhoid cases between 1999 and 2003 occurred in only one-third of the country's provinces – rural areas with unhygienic practices and poor water and sanitation systems (Figure 3).

These findings have important implications for typhoid fever immunization strategies at the country level, as they suggest that in many countries, vaccination in geographically-targeted, high-risk populations, rather than universal immunization, will be the most cost-effective means of controlling the disease.

Figure 3. Annual Incidence of Typhoid Fever among 5-14 Year Olds in Vietnam, by Province (1999-2003)



Source: Diseases of the Most Impoverished Programme

C. Trends in Antibiotic-Resistant Typhoid and Implications for the Control of Typhoid Fever

Outbreaks of multi-drug resistance (MDR) strains of *S. Typhi* – that is, resistance to all three of these first-line antibiotics (chloramphenicol, ampicillin, co-trimoxazole)– first appeared in the late 1980s in South Asia and the Middle East and rapidly spread to East Asia and Africa [29]. MDR typhoid has been associated with more severe illness and higher rates of complications and deaths, especially in children under two years of age [19,29].

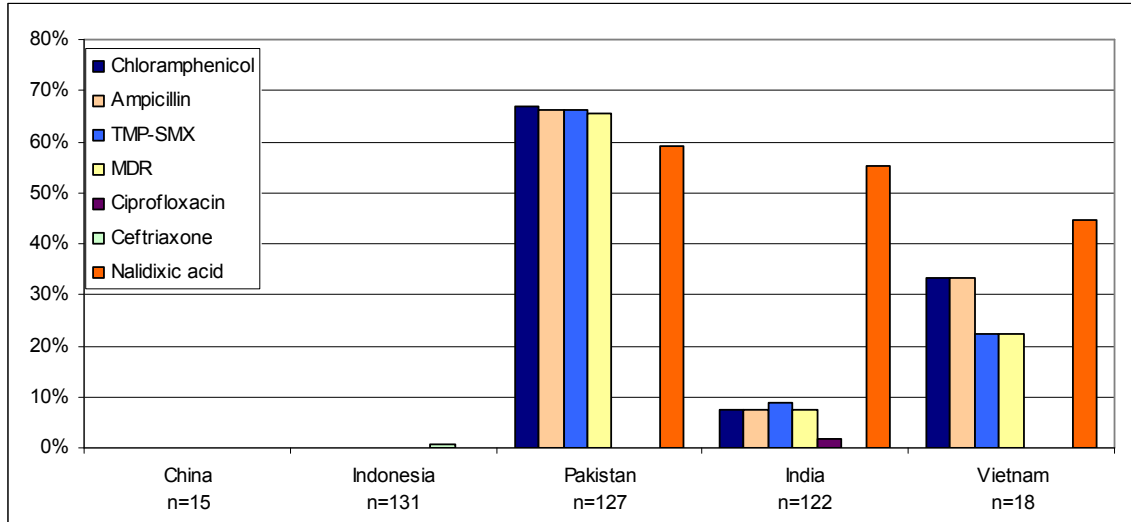
The emergence of multi-drug resistance *S. Typhi* strains has also led to the wide-spread use of fluoroquinolones, such as ciprofloxacin and ofloxacin, in countries where MDR is a problem. However, outbreaks of naladixic acid resistant typhoid (called NARST) started to occur in Vietnam and Tajikistan in the early 1990s and then spread to Pakistan and India [30].

Naladixic acid resistant typhoid cases respond less well to fluoroquinolones, exhibiting more prolonged fever than sensitive cases, and, in one study, a ten-fold higher rate of post-treatment stool carriage compared to sensitive cases (20% vs. 1.8%), increasing their potential to infect others [15]. Cases of full-blown resistance to ciprofloxacin were first reported in 2005 in Karachi and more recently in India (2007) (John Wain, unpublished data).

More recent data from the DOMI studies confirm that multi-drug and naladixic acid resistance is a serious problem in several sites (Figure 4), where 67% of isolates in Karachi, 22% in Hue and 7% in Kolkata were multi-drug resistant, and high rates of naladixic acid resistance were found in all three sites. Ciprofloxacin-resistant strains are now reported in India.

The dangers of growing resistance to more and more antibiotics include longer duration of the illness, fewer and more expensive treatment options (such as third-generation cephalosporins, which cost \$80-200 per course in Vietnam, vs. \$6-10 for oral first-line antibiotics), and higher case-fatality rates. The growth in antibiotic resistant typhoid is a key rationale stated by policymakers and experts for the need to introduce typhoid vaccination in high-risk areas.

Figure 4. Rates of Antibiotic Resistance among *S. Typhi* Isolates from Five Asian Study Sites in the DOMI Programme



MDR – resistant to chloramphenicol, ampicillin and co-trimoxazole (TMP-SMX)

Source: Diseases of the Most Impoverished Programme

D. The Economic Costs of Typhoid Illness

Recent data on the cost of typhoid illness have been obtained from the DOMI Programme in six Asian settings. The costs of illness among culture-confirmed patients in the five typhoid study sites were tracked, and a re-analysis of cost data from a typhoid surveillance study conducted in Delhi, India in 1995/96 was performed [14]. The costs of typhoid illness in the six studies were obtained in two ways:

- a. patients were interviewed at home at several time intervals following diagnosis to determine “private costs”, that is, the costs borne by families or other private entities (e.g., employers), including both direct costs paid out-of-pocket for medical treatment, drugs, laboratory testing, transportation, food and lodging (etc.), and indirect costs, such as lost wages due to work missed by the patient or his or her caretakers; and
- b. a micro-costing study at facilities used by the study patients at each site was conducted to estimate the “public costs” or costs from the health care perspective,

which involved estimating the average costs of a hospital-day or clinic visit, medicines and diagnostic tests in each site, as well as obtaining data from study patients on the number of inputs used (eg. hospital-days or clinic visits, etc)

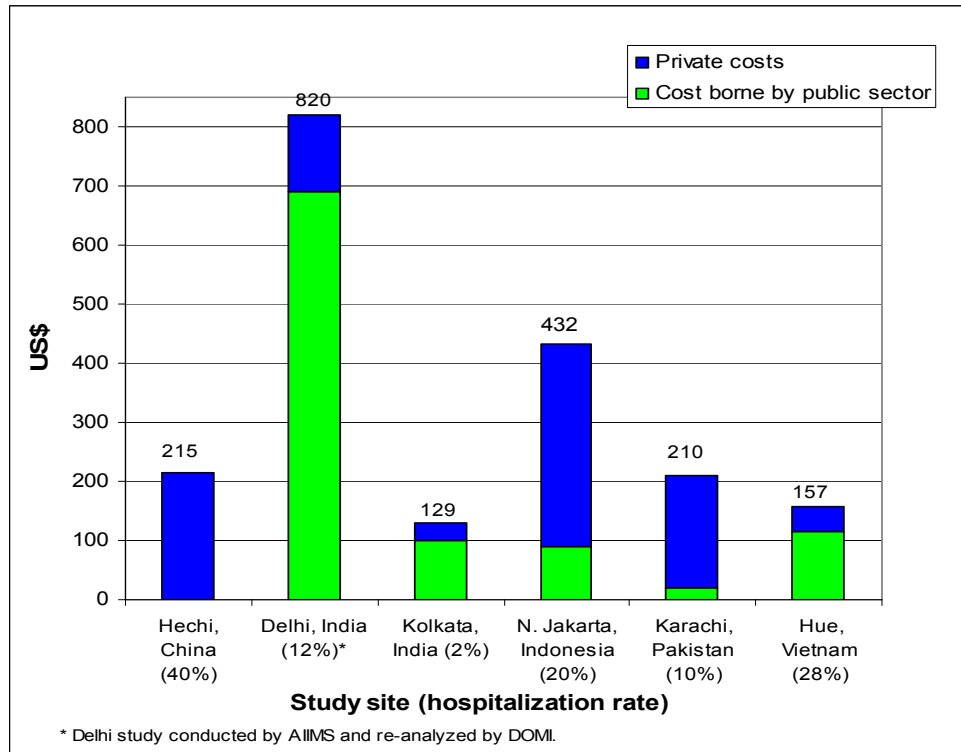
The average total (public and private) costs of hospitalized typhoid cases ranged from \$129 in Kolkata to \$820 in Delhi, India, and averaged \$334 across the six sites. Outpatient cases cost an average of \$13 to \$95. Using the hospitalization rates derived from the typhoid surveillance studies in each site¹⁰, the weighted average costs for all patients (hospitalized and non-hospitalized) ranged from \$15 in Kolkata to \$182 in Delhi, and averaged \$99 across sites.

The high average costs of hospitalized cases in Delhi were due in part to the high cost of treatment of patients who responded poorly to standard treatment with ciprofloxacin and who required expensive intravenous cephalosporins in hospital [14]. The costs of these illnesses, which likely were due to antibiotic resistant typhoid, were on average nearly four times greater than those who responded well to the first line of treatment.

Families bore the majority of costs of typhoid illness in all study sites, including most of the costs incurred by hospitalized cases in several sites (Figure 5). Families in North Jakarta, Karachi and Hechi paid on average \$342, \$191 and \$215, respectively, for hospitalized patients – mostly for out-of-pocket direct expenses. These average private expenses for hospitalized cases were the equivalent of 1.6 months of an average household income in North Jakarta and 1.2 months in Karachi. Clearly, typhoid illness can have a devastating financial impact on families in several of these largely poor communities.

¹⁰ With the exception of Karachi, Pakistan, where experts estimated a hospitalization rate of 10%, since DOMI patients received treatment in special study clinics and few required hospitalization, due to early detection and intervention (resulting from weekly home visits) and high levels of care on an outpatient basis.

Figure 5. Cost of Blood Culture-Confirmed Typhoid Illness for Hospitalized Cases (2005 US\$) in Six Asian Settings



Source: Diseases of the Most Impoverished Programme

III. Typhoid Prevention and Control Measures

Similar to other diseases spread by the faecal-oral route, typhoid fever predominates in areas with inadequate water and sanitation systems and/or poor hygienic practices. Typhoid was effectively eliminated in developed countries mainly through large-scale development of water treatment (*e.g.* chlorination and sand filtration), construction of deep wells and piped water and sewerage systems. Investment in provision of treated, bacteriologically-monitored water supplies and reliable methods from human waste disposal are the ultimate solution to control typhoid and paratyphoid fever, as well as most other enteric infections. However, it is likely that it will be many years until such water/sanitation improvement projects reach all of the large urban slums of Asian cities and endemic rural areas, where typhoid fever rates are highest. In the meantime, these populations will remain at high risk and will require other interventions to diminish the incidence of the disease.

Short of major improvements in water-sanitation infrastructure, a number of other selective interventions have been found to be effective as low cost alternatives to large-scale infrastructure projects in reducing diarrhoeal disease incidence in developing countries. Intensive hygiene education, such as promoting hand washing using soap, discouraging open de-faecation by children, and the proper disposal of garbage and faeces, has been shown to reduce diarrhoeal disease incidence in young children [31,32].

Similarly, several interventions aimed at improving the quality of water at the household level – where even clean water often becomes contaminated during storage and use – have also been implemented in recent years through the CDC/PAHO's Safe Water System programme and other projects and have shown some promising results. These point-of-use interventions have been shown to reduce diarrhoeal disease incidence in households by 20-30% in several studies in several pilot programmes [33].

Vaccination using new-generation typhoid vaccines provides another option to prevent the disease in the short- or medium-term. There is evidence that typhoid immunization can virtually eliminate typhoid fever in a relatively short period of time, especially when targeted towards

high-risk age groups and geographic areas. Vaccination also does not require significant behavioral change, and as vaccine prices have decreased, it is becoming more affordable to governments and increasingly cost-effective. Most policymakers and experts, however, believe that provision of typhoid vaccination should be part of a package that includes hygiene education messages, community or national food hygiene measures, sanitation improvements (*e.g.* latrines) and improved water supply and quality measures.

Interventions to Control Typhoid Fever

- Community/national measures:
 - Quality control for food industry and shellfish sanitation
 - National efforts to improve sanitary food preparation (including requirements for food handlers to be vaccinated)
 - National efforts to improve boiling / pasteurization of milk and dairy products
- Water systems:
 - Piped water and other infrastructure improvements
 - Treatment of water (chlorination)
 - Point-of-use household interventions (packaged chlorine solutions, filtration, improved water storage containers (*e.g.*, with spigots or narrow mouths)
- Sanitation:
 - Sewerage systems
 - Latrines at household level
- Hygiene education:
 - Promotion of handwashing with soap
 - Discourage open de-faecation by children
 - Proper disposal of faeces and garbage
- Training of health care workers and preparation of guidelines for the diagnosis and treatment of typhoid to increase appropriate case management
- Vaccination using new-generation vaccines

IV. The Case for Targeted Typhoid Immunization using New-Generation Vaccines

A. Composition, Safety and Immunological Properties of the Currently-Licensed New-Generation Typhoid Vaccines

Key points

- There are two licensed and internationally available typhoid vaccines, which have been demonstrated to be safe and efficacious in several large scale randomized, placebo-controlled studies in endemic countries.
- The currently licensed liquid formulation of Ty21a (the likely formulation to be used in developing countries) has shown protective efficacy of 53% - 78% in children in large-scale randomized, placebo-controlled studies, conferring protection for at least five years.
- Vi polysaccharide vaccine showed protective efficacy of 64-72% in randomized placebo-controlled studies in children and adults in endemic countries. The vaccine confers protection for at least three years.
- Both vaccines are licensed for use in persons two years and older, although data are limited on the clinical protection conferred by the vaccines to children less than five years of age.

The two new-generation typhoid vaccines that are currently internationally licensed and available are the injectable Vi polysaccharide vaccine and the oral, live attenuated Ty21a vaccine. A summary of their main characteristics is shown in Table 1.

Table 1. Summary of the Characteristics of the Two Currently-Licensed New-Generation Typhoid Vaccines		
Characteristic	Vi polysaccharide	Ty21a
Vaccine type	Subunit	Live attenuated
Composition	Purified Vi capsular polysaccharide of the Ty2 <i>S. Typhi</i> strain	Chemically-mutated Ty2 strain of <i>S. Typhi</i>
Immunogenic properties	<ul style="list-style-type: none"> ▪ Elicits serum IgG Vi antibodies ▪ T-cell independent (no booster response) 	<ul style="list-style-type: none"> ▪ Elicits mucosal IgA and serum IgG antibodies against O, H and other antigens, as well as cell-mediated responses ▪ No booster effect has been shown
Route of administration	Parenteral (subcutaneous or intramuscular)	Oral
Minimum age at which vaccine is licensed for use	Two years old	Two years old for liquid formulation and five years old for capsule formulation
Formulation	Solution of 25 µg combined with buffer	<ul style="list-style-type: none"> ▪ Enteric-coated capsules, or ▪ Liquid suspension (lyophilized vaccine + buffer mixed with water upon use)
Number of doses required for complete vaccine regimen	One	Three to four
Storage requirements	Requires storage at 2°-8°C	Requires storage at 2°-8°C
Safety/tolerability	High	High
Length of protection	At least 3 years	At least 5-7 years
Can be co-administered with other vaccines?	Yes	Yes

A.1. Vi polysaccharide vaccine

Vi is a subunit vaccine consisting of the purified Vi (“virulent”) polysaccharide outer capsule of the Ty2 strain of *S. Typhi*. The vaccine is administered subcutaneously or intramuscularly as a single dose of 25 µg. It was first developed in the 1970s and further developed for large-scale manufacture by Dr. John Robbins’ laboratory at the U.S. NIH, in collaboration with Pasteur-Merieux-Connaught (now Sanofi Pasteur). First licensed in the U.S. in 1994, the vaccine is in the

public domain (i.e., no patent protection) and is now being produced by several multi-national and developing country manufacturers.

Like other T-independent purified polysaccharide vaccines, such as meningococcal and pneumococcal vaccines, Vi does not elicit adequate immune responses in children under two years of age, and thus is licensed for use in persons two years and older. The vaccine is highly heat stable and is able to retain its physicochemical characteristics for six months at 37°C and for two years at 22 °C (room temperature).

Vi vaccines have been extensively tested in humans and demonstrate a strong safety profile. No serious adverse events and minimum side effects were associated with Vi vaccination of more than 11,000 children in South Africa [34], almost 7,000 individuals 5-44 years of age in Nepal [35] and approximately 130,000 subjects 3-50 years of age in China [36]. Of the 22 million doses of Vi that PMC (now Sanofi Pasteur) distributed from 1989 to 1996, only 20 serious adverse events and 120 non-serious events were reported to the manufacturer [16]. Vaccination of nearly 195,000 individuals in the five Asian sites of the DOMI Programme have confirmed the minimum side effects associated with administration of Vi vaccine. Vi has also been shown to be well tolerated and safe when co-administered with other oral or injectable vaccines [16]. In a recent study conducted in China [37 in press], Vi re-vaccination two years after the first dose in children aged 9-14 was shown to be safe.

Parenteral Vi vaccine elicits serum IgG Vi antibody responses in 85 to 95% of adults or children older than two years of age. Purified Vi polysaccharide behaves like a T-lymphocyte-independent antigen, and thus, the serum antibody response is not boosted by additional doses [38]. A second dose of Vi given by Keitel and colleagues, 27 to 34 months after a primary inoculation stimulated four-fold rises in serum Vi antibody titer in 33 to 50% of subjects [39]. However, the titers returned only to the levels achieved one month after the primary immunization. Titers of Vi antibody progressively fall over time [39]. Klugman has proposed that a serum Vi antibody titer of greater than or equal to 1.0 µg per mL be considered to confer protection [40]. No interference has been shown when co-administered with other vaccines,

including hepatitis A, meningococcal, IPV, diphtheria and tetanus toxoids, MMR, hepatitis B, and yellow fever [3,16].

Results of Vi efficacy trials conducted in typhoid-endemic countries are shown in Table 3. In a randomized double-blinded controlled efficacy trial involving more than 11,000 South African children, Klugman and colleagues found that one dose of Vi vaccine (25 µg) was 64% efficacious after 21 months, declining to 55% three years following vaccination [40]. More than 50% of Vi-vaccinated children were noted to have protective levels of serum anti-Vi antibodies ten years after vaccination [41]. In Nepal, a randomized controlled efficacy study in 6,900 subjects 5-44 years old conducted by Acharya and colleagues showed that administration of a single dose of Vi vaccine conferred 72% efficacy in vaccinees after 17 months of follow-up [35]. Finally, a double-blinded, randomized field trial in Guangxi Zhuang Autonomous Region in southwestern China, using 30µg dose of a locally produced Vi and involving 131,000 persons 5-30 years of age, found the vaccine to be 69% protective against blood culture-confirmed typhoid over 19 months, and 72% in school-aged children [42]. A study of the longer term efficacy of locally-produced Vi in two counties in China showed evidence of approximately 50% protection during the third year of follow-up after vaccination [42]. Vi is therefore considered to be protective for at least three years.

A.2. Ty21a

Ty21a is an orally administered, live-attenuated Ty2 strain of *S. Typhi* in which multiple genes have been chemically mutated, including those responsible for the production of Vi. The vaccine, developed in the 1970s and first licensed in 1989, is produced mainly by Crucell Holland A.V. (formerly, Berna Biotech) and sold under the trade name of Vivotif®. A second, more recent producer is Boryung in South Korea.

This lyophilized vaccine is currently available in two formulations:

- a. enteric-coated capsules, which are given in 3-4 doses, and
- b. a liquid suspension consisting of the vaccine in one sachet and a buffer in another, which are combined with water before administration. The liquid formulation is given in three doses.

For both formulations, the doses are administered every other day (e.g. over a five-day period). The capsule formulation is licensed for persons five years and older, while the liquid formulation can be given to persons two years and above. While the capsules are often used for travelers to developing countries, the liquid formulation is the one most likely to be used by public health programmes for immunizing young children in developing countries. The vaccine requires a cold chain (at 2° - 8°C) and survives for approximately 14 days at 25°C.

Ty21a vaccine has been shown to be well-tolerated and to have low rates of adverse events. In three double-blinded, randomized placebo-controlled efficacy trials in Chile and Indonesia involving approximately 325,000 school children, reactogenicity of the Ty21a vaccine was assessed through active surveillance. The rates of side effects (diarrhoea, vomiting, fever and rash) in the vaccinated groups were not found to be significantly greater than those in the control groups for both the enteric-coated capsule and liquid formulations [3].

In large-scale field trials in children in Egypt, Chile and Indonesia, Ty21a was found to have protective efficacy rates against blood culture-confirmed typhoid fever of 33-67% for the enteric-coated capsules and 53-96% for the liquid formulation (53-78% for the currently licensed liquid formulation) after three years of follow-up, when each was given in three doses every other day (except in Indonesia, where dosing occurred every 7 days) [3] (Table 2). The vaccine appeared to be more efficacious in areas with lower incidence of typhoid (Egypt, Chile) than in hyper-endemic areas, such as Indonesia. A large trial in Chile also indicated that a fourth dose of the vaccine significantly increased the protective effect of the capsule formulation – with those in the 4-dose group having a 60% lower incidence rate than those who received two or three doses (96/100,000 vs. 161/100,000) [3]¹¹. In two trials in school-aged children in Chile with long-term follow-up, the enteric-coated capsule version was found to still be 62% protective after seven years (vs. 67% at three years) and the liquid formulation was shown to be 78% protective at five years (vs. 77% at three years). Ty21a is therefore considered to provide protection for at least five to seven years.

¹¹ The PE for the 4-dose regimen could not be calculated since there was no control group in this trial.

Large-scale vaccination with Ty21a also appeared to confer herd protection in Chile [43]. In children within the placebo group in a field trial in Area Norte, Santiago, the incidence of typhoid progressively fell each year as each of three field trials was initiated in subsequent years in other administrative areas of the city. The incidence rate in this group diminished by approximately 70% from the mean incidence in the three years before the trials [43]. These data suggest that the systematic application of live oral typhoid vaccine can notably reduce the incidence of the disease in endemic areas.

In addition, in randomized, controlled field trials in Area Norte and Area Occidente in Santiago, Chile, two or three doses of Ty21a in enteric-coated capsules showed protection against *S. enterica* serovar Paratyphi B disease (56% efficacy in Norte after two doses [44]; 42% efficacy in Occidente after three doses) [45].

Table 2. Results of Randomized Controlled Clinical Trials of New-Generation Typhoid Vaccines							
Study (Year)	Formulation	No. Study Participants	Ages (Years)	Control Vaccine	Follow-up Period	Protective Efficacy for Blood Culture Confirmed Typhoid (95% CIs)	Typhoid Incidence Rate in Control Group (per 100,000)
Ty21a:							
Alexandria, Egypt (1978-80)	Liquid given with tablet of NaHCO ₃ ¹²	32,388	6-7	Placebo	36 months	96% (77-99%)	50
Area Occidente, Santiago, Chile (1983-86)	3 doses of enteric-coated capsules given (1-2 days between doses)	140,000	6-19	Placebo (plus 4 vaccine groups that varied in formulation and time interval between doses)	36 months	67% (47-79%)	110
					7 years	62%	
Area Sur Oriente, Santiago, Chile (1986)	3 doses of enteric-coated capsules (1-2 days betw doses)	81,321	6-19	Placebo	3 years	33% (0-57%)	100
	3 doses liquid suspension (1-2 days betw doses)				3 years	77%	
					5 years	78%	
Sumatra, Indonesia (1986-1989)	3 doses of enteric-coated capsules (7 days betw doses)	20,543	3-44	Placebo	30 months	42% (23-57%)	810
	3 doses liquid suspension (7 days betw doses)					53% (36-66%)	

¹² This formulation is not commercially on the market.

Table 2. Results of Randomized Controlled Clinical Trials of New-Generation Typhoid Vaccines							
Study (Year)	Formulation	No. Study Participants	Ages (Years)	Control Vaccine	Follow-up Period	Protective Efficacy for Blood Culture Confirmed Typhoid (95% CIs)	Typhoid Incidence Rate in Control Group (per 100,000)
Vi polysaccharide:							
Kathmandu Valley, Nepal (1986-1988)	1 dose of Vi (25 µg)	6,907	5-44	Pneumococcal polysaccharide	17 months	72% (42-86%)	926
E. Transvaal, South Africa (1985-1988)	1 dose of Vi (25 µg)	11,384	6-14	Meningococcal A/C polysaccharide	21 months 36 months	64% (36-79%) 55%	773
Quan County, Guangxi Province, China (1995-1997)*	1 dose of locally-produced Vi (30 µg)	131,271	3-50 (92% school-age)	Saline placebo	19 months	69% (28-87%) (72% in school children)	63-78
Sources: Levine 1999 (3); Ivanoff, Levine, Lambert, 1994 (4); Simanjuntak, 1991; Hessel et.al., 1999 (16); Klugman et al. 1987 (42); Acharya et.al., 1987 (43); Yang et.al., 2001 (44); Acosta et. al., 2005 (51)							

*Note: An earlier efficacy study of Vi in China (1994-95) was a double-blinded, randomized, saline placebo control study among 81,000 5-55 year olds in Boaying County in Jiangsu Province. The efficacy at 12 months was 71% (95% CI 33-88%) (published in Chinese: Wang ZG, Zhou WZ, Shi J. Efficacy and side effects following immunization with *Salmonella typhi* Vi capsular polysaccharide vaccine. *Zhonghua Liu Xing Bing Xue Za Zhi* 1997;18(1):26-9.).

B. The Supply, Potential Demand for, and Price of Typhoid Vaccines: Current Situation and Future Trends

Key points

- There are currently several vaccine manufacturers in both the developed and developing world producing new-generation typhoid vaccines, with more producers coming onto the market in the near future.
- While no typhoid vaccine has yet been pre-qualified by WHO, there is the potential for typhoid vaccines produced by several manufacturers to be pre-qualified, including both Vi and Ty21a.
- The potential production capacity of typhoid vaccines can easily meet the potential increased global demand, if the vaccines are introduced more broadly into endemic countries.
- The prices of new-generation typhoid vaccines have dropped significantly over the past decade (e.g., to ~\$.050 or less for Vi) and further price declines are possible as demand and competition increase.

B.1. The supply of Vi and Ty21a vaccines

When the WHO recommendations regarding typhoid vaccines were made in 2000, there were only two international producers of Vi polysaccharide vaccine – Pasteur-Merieux-Connaught (now Sanofi Pasteur) and SmithKline Beecham (now GSK Biologicals). Vi was also being produced in China by several state-run producers for domestic use. The producer of the oral, live attenuated Ty21a was Berna Biotech. The main markets for these vaccines (outside of China) consisted of travelers from industrialized countries visiting typhoid-endemic countries, and private sector patients in developing countries. Retail prices in the private sector for each vaccine averaged \$6.00 - \$8.00 in Vietnam, Bangladesh and Pakistan, and were higher for Vi in Indonesia (\$16-25 with a consultation fee) [46].

In the years since the WHO recommendation, several developing country manufacturers have acquired the technology to produce Vi, including Bharat Biotech and BioMed in India, Finlay

Institute in Cuba and IVAC in Vietnam (Table 3). This proliferation of Vi producers has been facilitated by technology transfer from the U.S. National Institutes of Health (NIH) to several companies, the lack of patent protection, as well as the relative simple, low-cost production process involved. Bharat markets its Vi vaccine both within India and to other countries, and BioMed, Finlay and IVAC sell Vi vaccines to their domestic markets in India, Cuba and Vietnam, respectively.

Two additional developing country producers – BioFarma in Indonesia and Shantha Biotechnics in India – are in the process of developing Vi vaccines, in collaboration with the US NIH and the International Vaccine Institute (IVI). Both producers plan to have their Vi vaccines licensed within the next two to three years.

Table 3. Current and Future Producers of Vi Vaccine			
Producer	Country of Origin	Brand Name	Current and Potential Market Focus
Sanofi Pasteur*	France	Typhim Vi	International
GlaxoSmithKline (GSK)*	Belgium	Typherix	International
Bharat Biotech	India	Typbar Vi	International and domestic
BioMed	India	Typho-Vi	Domestic market
Finlay Institute	Cuba	Vax-TyVi	Domestic market
IVAC	Vietnam		Domestic market
Beijing Institute	China	N/A	Domestic market
Chengdu Institute	China	N/A	Domestic market
Wuhan Institute	China	N/A	Domestic market
Changchun Institute	China	N/A	Domestic market
Shantha Biotechnics* (in the near future)	India	N/A	Domestic and international
BioFarma* (in the near future)	Indonesia	N/A	Domestic and international
* Producers of WHO pre-qualified vaccines			

As for Ty21a production, Boryung of South Korea is now producing the vaccine, in addition to Berna Biotech (a Crucell company). This vaccine is no longer patent protected, opening up the possibility of technology transfer arrangements with other producers in the future.

To date, no typhoid vaccine has been pre-qualified by WHO, since these vaccines have yet to be targeted for purchase by UN agencies. However, if the introduction of typhoid vaccines in

endemic countries becomes a higher priority within the global health community, there is the potential for several producers to become WHO pre-qualified for Vi and Ty21a and thus able to contribute to the global supply.

B.2. Production capacity, potential demand for and prices of typhoid vaccines

While precise estimates of the global sales for typhoid vaccines are not readily available, discussions with various vaccine producers indicate that the current sales volume is around 20 to 30 million doses per year, with developing country producers accounting for up to two-thirds of this volume. Vi makes up an estimated 95% of the global market, and Ty21a, the remaining 5%. However, the global production capacity of Vi vaccine is under-utilized and could be increased to many times the current production volume, without the need for additional capital investments, if the current Vi vaccine producers increased their production volume by simply increasing the number of batches they produce at existing facilities. Crucell, the main producer of Ty21a, has also indicated that it could substantially increase production if there was increased demand for the vaccine from developing countries.

As to the potential demand, a preliminary estimate was calculated for 30 countries in Southern Africa, South, Central and Southeast Asia – regions considered to have high typhoid incidence (>100/100,000 per year) [2] (see Appendix 1). Assuming that 80% of 5-14 year old children living in urban areas were vaccinated with Vi every three years in all 30 countries – which include the large countries of India, Indonesia and Pakistan – the estimated number of doses required each year, including wastage, would be approximately 136 million doses. This estimate is likely to be high, since it assumes that the vaccine would be introduced in all Indian cities – an unlikely assumption – and it includes Vietnam, which is self-producing for Vi. Nonetheless, the supply of typhoid vaccine does not appear to be a problem with manufacturers being able to meet the increased demand for new-generation typhoid vaccines, when and if they are introduced into public health programmes in endemic countries.

Of course, to fully realize the potential demand for typhoid vaccines and the impact of their introduction requires that better surveillance systems for incidence and prevalence data on enteric fever be established.

The price of Vi has also declined sharply since 1998, as more and more developing country producers have entered the market. Several developing country producers of Vi are now offering prices to the public sector of about \$0.50/dose for a multi-dose vial presentation. The multi-national Vi producers have also indicated their willingness to offer competitive prices for public sector programmes in the developing world. Crucell has also signaled its interest to offer competitive and tiered prices for Ty21a to developing country governments. With increased demand and more producers coming onto the market, there is a potential for even further price declines, as well as tiered pricing by the international producers.

C. Population Acceptance, Feasibility of and Demand for Typhoid Vaccination in Endemic Countries

Key points

- Typhoid fever is a well recognized health problem by local populations, especially in areas with high disease burden.
- Results of socio-behavioral and private demand studies in five Asian settings with endemic typhoid indicate considerable population demand for new-generation typhoid vaccines.
- The feasibility and population acceptance of both community- and school-based typhoid vaccination using new-generation vaccines have been demonstrated in several pre-licensure clinical trials (of Ty21a) and post-licensure demonstration projects (of Vi).

Three types of information provide insights into the potential demand for, and acceptance and feasibility of typhoid vaccination amongst populations living in typhoid-endemic areas, including impoverished (urban slum) areas. These are:

- a. results from the DOMI socio-behavioral household surveys in five Asian study sites on the knowledge, perceptions, and practices regarding typhoid fever and the public interest in vaccination, which were conducted prior to, and after, Vi vaccination demonstration projects that took place at each site;

- b. vaccination coverage rates from the DOMI post-licensure Vi demonstration projects and large school-based pre-licensure studies of Ty21a conducted in Santiago, Chile; and
- c. data on the demand and willingness-to-pay for typhoid vaccines from private demand surveys conducted by DOMI in both low- and middle-income neighborhoods prior to the Vi demonstration projects in Asia.

C.1 Socio-behavioral study results

Research suggests that vaccine acceptance or demand can be influenced by the perceived prevalence of the disease in the community [47], as well as by beliefs regarding the severity of the disease, the risk of its striking one's household, attitudes towards vaccination in general and perceived benefits and risks of specific vaccines, among other factors [48].

Socio-behavioral studies of 500-1,000 randomly selected households in each of the five DOMI study sites conducted prior to the typhoid information campaigns and Vi demonstration projects showed that knowledge of the disease, perceived prevalence and perceived risk were generally high in the sites with high incidence of typhoid fever (*i.e.* Kolkata, India Karachi, Pakistan and North Jakarta, Indonesia) and lower in the relatively low incidence sites of Hue, Vietnam and Hechi, China. While most respondents across sites claimed to have knowledge about typhoid fever, 31-48% of families reported having past experience with typhoid in their households in Kolkata, Karachi and North Jakarta. Sixty-six percent of respondents in Jakarta and 52% in Karachi felt it was “very likely” that someone in their household could get the illness in the future. Nearly all respondents across sites believed that typhoid fever is a “serious” or “very serious” disease in children.

High-risk communities also demonstrated good knowledge of how to prevent typhoid fever. Responses concerning “good typhoid prevention measures” in Karachi and North Jakarta were highest for effective measures, such as eating clean food, boiling water, avoiding street food and washing hands. In addition, across both high and low incidence sites, vaccination received the greatest number of responses as a good preventive measure.

C.2. Vaccination coverage rates for typhoid vaccines in Vi demonstration projects and Ty21a clinical trials

Post-licensure Vi demonstration projects were conducted in five typhoid study sites – selected slum areas in Kolkata, Karachi and North Jakarta, and the entire cities of Hechi, China and Hue, Vietnam. The vaccination campaigns, involving more than 194,000 persons in all, were school-based in North Jakarta and Hue, and community-based in Karachi, Kolkata and Hechi. Vaccination was limited to children in North Jakarta, Karachi and Hue, but targeted to both children and adults in Hechi and Kolkata. Multi-faceted information campaigns preceded the vaccination campaigns in each site.

Vaccination coverage rates in the five demonstration sites ranged from 58% in Hue to 91% in North Jakarta, and averaged 73% across sites (Table 4). The relatively low coverage rate in Hue was found to be due to negative publicity from the media about the experimental (randomized, controlled) design of the study. In fact, four of the five demonstration projects (Hechi, Kolkata, Karachi, and Hue) had randomized, controlled study designs and, accordingly required written informed consent for participants, a feature that likely depressed coverage rates in these sites. Nonetheless, 68-69% of the targeted populations in the slums of Kolkata and Karachi were successfully vaccinated through community-based campaigns. Moreover, the one project, in Jakarta, in which Vi vaccine was given as a routine public health intervention rather than as an arm of a randomized, controlled project, demonstrated an extremely high coverage rate of 91%. These results suggest that, despite the need to provide the vaccine outside of the infant EPI schedule, substantial typhoid vaccination coverage levels can be achieved either in schools or in the communities, even in predominantly poor slum areas, if accompanied by well-conceived social mobilization campaigns.

Similar results for the feasibility and the acceptability of the Ty21a vaccine were observed in Santiago, Chile, where the vaccine was administered to almost half a million school aged children through large school-based, randomized, controlled vaccine trials [45]. Population acceptance was generally high, and the vaccination was carried out without the need for medical supervision. More studies of Ty21 acceptability and compliance are being planned in Zambia.

Table 4. Vaccination Coverage Achieved in DOMI Vi Vaccination Projects					
Data	Hechi, China	Kolkata, India	N. Jakarta, Indonesia	Karachi, Pakistan	Hue, Vietnam
Type of demonstration project	CRCT*	CRCT	Demonstration project (no controls)	CRCT	CRCT
Type of setting	Urban and rural	Urban slum	Urban slum	Urban slum	Urban
Setting	Community-based	Community-based	School-based	Community-based	School-based
Target ages (years)	5-60	≥2	≈6-12 (Grades 1-5)	2-15	≈5-18 (Grades 1-12)
No. persons vaccinated	92,476	37,687	4,828	27,236	32,267
Percent coverage of the target population	78%	69%	91%	68%	58%
* Cluster randomized, controlled trial					

C.3. Results from private demand studies of typhoid vaccines

The demand for new-generation typhoid vaccines among these populations was also measured in surveys of private demand, using formal contingent valuation methodology, that took place among randomly-selected households in both low- and middle-income areas. The surveys assessed willingness to pay for a vaccine with the characteristics of Vi. The average amount respondents living in low-income areas were willing to pay for such a vaccine for their children ranged from \$2 in Kolkata, India to \$16 in Guilin, China. Forty percent or more of respondents in the China, India, Pakistan and India study sites were willing to pay at least \$2.00 for their child to get vaccinated. As expected, willingness to pay for vaccine was higher in non-poor than poor households. These data highlight the high demand for typhoid vaccine in all of the study sites, including those (Hechi and Hue) in which the incidence of typhoid fever was not high. The greater willingness of non-poor than of poor households to pay for vaccine suggests that cross-subsidization schemes, whereby users' fees from wealthier households are used to subsidize free immunization of poor households, may be viable financing strategies in some countries.

D. Effectiveness and Impact of Typhoid Vaccination on Clinical Disease

Key points

- Systematic use of Vi vaccine through the public health system in Guilin, China appears to have reduced the incidence of endemic typhoid to very low levels.
- Evidence from China shows that Vi vaccination is equally effective in controlling currently-occurring typhoid outbreaks as in reducing endemic disease.
- Pre-licensure trials of Ty21a in Santiago, Chile, in schoolchildren, which employed school-based immunization that simulated public health practice, found the vaccine to be safe and protective and to confer herd protection

D.1 Effectiveness and impact of Vi vaccines

The protective efficacy of Vi vaccines in randomized controlled trials has been shown to be around 70%, and protection has been shown to last at least 3 years. However, the actual impact of a vaccine in public health programmes may differ from that measured in pre-licensure trials due to the vagaries of cold chain storage, vaccination coverage and other aspects of such programmes. Conversely, the impact of a vaccine in public health programs may be greater than predicted on the basis of clinical trials, due to herd protective effects that are typically not measured in pre-licensure trials.

Evidence of the actual impact of Vi vaccination implemented under real-life conditions comes from Vi vaccination programs in some provinces in China, which provide evidence of the effectiveness of Vi in controlling both endemic and epidemic typhoid.

a) Vi vaccination programmes in China and Central Asia

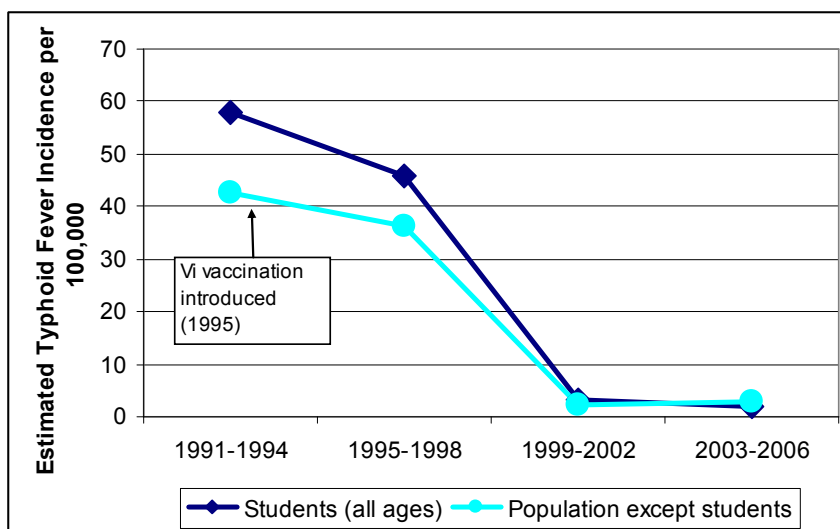
(i) Evidence of impact of Vi introduction on incidence of endemic typhoid

A programme of Vi vaccination began in 1995 in the city of Guilin in Guangxi Province, China, with a total population of around 2.5 million people [49]. The programme targeted school students of all ages, food handlers, and people living in and around areas where

outbreaks occurred. Re-vaccination has taken place every three years. From 1995 to 2006, more than 1.4 million doses of Vi were administered, with 77% going to students and 23% going to food handlers and residents of outbreak areas. Coverage rates have varied broadly from year to year, but have averaged 60-70% for students over the 11-year period and 80-85% for the other target groups.

The incidence of typhoid fever reported in the city averaged 47/100,000 in the overall population and 61/100,000 in students from 1991-94, before Vi vaccination began. The incidence has declined to very low levels (0.2 – 4.5/100,000) in both the student and general population from 1995 to 2006 (Figure 6). This decline could be due to other factors besides the vaccination programme, such as economic development and improvements in water and sanitation during this period. However, two facts suggest that the vaccination programme played a major role in the sharp reduction of typhoid fever incidence in Guilin. First, water and sanitation improvements in Guilin have been quite gradual during this period. Secondly, incidence rates of enteric fever due to *S. Paratyphi A*, which is also caused by poor water and sanitary conditions, actually *increased* in Guilin during the same period [49].

Figure 6. Incidence of Reported Typhoid Fever in Guilin Before and After the Introduction of Vi Vaccination



Source: Yang, 2007 (ref 49)

(ii) Effectiveness of Vi vaccine in controlling outbreaks

At the beginning of an outbreak of typhoid fever that occurred among students attending a middle school in 1999 in Xing-An County, Guangxi Province in Southwestern China, Vi vaccination was provided to students who had not been vaccinated with Vi the year before during a school-based campaign [50]. Vaccination early on in the outbreak, using a locally-produced Vi vaccine, was associated with a vaccine effectiveness of 71% – nearly as much as the vaccine efficacy among those whom had been vaccinated with Vi the year before (73%). This study suggests that the single-dose Vi vaccine is effective for outbreak control, as well as for use against endemic disease.

A mass vaccination campaign involving almost 20,000 Russian soldiers stationed in Dushanbe, Tajikistan during the large epidemic of typhoid fever in 1996 and 1997, demonstrated the effectiveness of the vaccine in reducing typhoid disease among these individuals who were affected by inadequate food, water and general living conditions during the outbreak [24].

D.2 Effectiveness and Impact of Ty21a

Ty21a vaccine has thus far been limited to use primarily for travelers and has not been used by developing countries for control of endemic typhoid. However, it is worth noting that the large-scale pre-licensure trials of this vaccine done in several hundred thousand Chilean schoolchildren (Table 2) employed classrooms as the unit of randomization, much as would occur in a practical school-based immunization programme. Indeed, the trial in Area Sur and Area Central of Santiago was undertaken as a post-licensure effectiveness trial that represented a collaboration of the Ministry of Health and Ministry of Education undertaking a school-based immunization program that targeted ~ 225,000 school children.

As shown in the table, the controlled field trials in Chile and Indonesia found the Ty21a vaccine to be efficacious and to confer several year-protection for 5-7 years. Moreover, as noted earlier,

Ty21a was also found in the Chilean to be associated with herd protection of non-vaccinees in these studies.

In addition, a large randomized, placebo controlled study of Ty21a conducted in 6-7 year old school children in Alexandria, Egypt showed efficacy of 96% after three years [51]. The study was the first to show the efficacy and practicality of a liquid formulation (the lyophilized vaccine was reconstituted with diluent for consumption by the young children).

E. Cost-effectiveness of typhoid vaccination

E.1 Vi vaccination costs

A recent cost-effectiveness analysis of Vi typhoid vaccination has been conducted, based on multi-faceted data from the DOMI studies [Cook J et al, (submitted)]. The analysis estimated cost-effectiveness ratios for four study sites (Kolkata, India; North Jakarta, Indonesia; Karachi, Pakistan and Hue, Vietnam), using site-specific data on: age-specific incidence rates of typhoid fever, cost of typhoid illness, private demand for typhoid vaccines (to estimate expected vaccine coverage rates) and the cost of typhoid Vi vaccination.

Assumptions for the base case estimates (with the range for the sensitivity analyses) include the following.

- A case fatality rate of 1% [0.5% - 3%]
- A DALY weight of 0.27 [0.075 – 0.471], which lies within a range of weights for somewhat similar diseases (malaria, Japanese encephalitis, dengue, upper respiratory infections) [62]
- Vaccine effectiveness of 65% [55% - 75%]
- Duration of protection of 3 years [2 – 4 years]
- A vaccine cost \$0.57 per dose, including \$0.45 for the vaccine price per dose for multi-dose vials, based on recent quotations from high-quality Vi producers in India; 15% shipping and handling costs; and 10% wastage
- A cost of \$0.50 to delivery/administer the vaccination in Kolkata, Hue and Karachi (low-income countries) and \$1.00 in North Jakarta (middle-income)

The analysis estimates the cost-effectiveness of three immunization program options over a three-year period (the assumed duration of Vi):

1. school-based immunization for 5-14 year olds attending school;
2. school-based vaccination for both school-aged (whether attending school or not) and pre-school children, that is for all 2-14 year olds, using the schools as vaccination points; and
3. community-based vaccination of all eligible children and adults (2 years and older) in the two study sites where adults were included in the DOMI disease surveillance (Kolkata and North Jakarta).

The analysis used the WHO definitions of “cost effective” and “very cost effective”, that is, an intervention that has a cost per DALY averted that is less than the GDP per capita is “very cost effective”, and one with a cost per DALY averted that is less than three times the GDP per capita is “cost effective”. All programme options were found to be “very cost effective” in the high-incidence study sites of Kolkata, Karachi and North Jakarta. Vaccination of school children (Option 1) was generally the most cost-effective option, with a cost per DALY averted of \$177 in Kolkata, \$220 in Karachi and \$645 in North Jakarta. However, vaccinating pre-schoolers as well as school children increased the cost-effectiveness ratios in Kolkata and Jakarta only slightly and actually lowered the ratio in Karachi, due to the very high typhoid incidence rates among 2-4 years found in that site. These results argue for including pre-schoolers in typhoid vaccination programmes in high incidence settings, such as these, for economic as well as moral reasons.

Vaccinating adults of all ages, as well as children in the Kolkata and North Jakarta study sites (Option 3) increased the cost-effectiveness ratios by up to 2.5 times, but was still found to be “very cost-effective” in both sites.

Typhoid vaccination was not found to be cost-effective in Hue, Vietnam, where typhoid incidence was found to be relatively low. However, the situation would be quite different in parts of the country where typhoid incidence continues to be high, such as in the Mekong Delta and Northwest corner of the country (see Figure 3).

Sensitivity analyses that varied the assumptions for typhoid incidence, vaccination cost, case fatality rates, the level and duration of protection of the vaccine did not in most cases change the overall assessment of whether the program was “very cost effective” in the three high-incidence sites, especially the programs focusing on children.

E.2 Ty21a vaccination costs and cost effectiveness

Feasibility of administration of the capsule formulation has been well demonstrated in school aged children during the clinical trials in Chile (n=250,000). Acceptance was generally high, and the implementation was carried out without the need for medical supervision. Several studies of compliance have been carried out in travelers which show good acceptance. More recent studies in acceptability and compliance are planned in Zambia.

Cost of vaccination will be cost of vaccine plus wastage and logistics, without the need for medical supervision and specialized sharps destruction the overall costs should be comparable with Vi vaccines.

V. Typhoid Vaccines under Development

Key points

- Several efforts are underway to develop low-cost Vi conjugate vaccines for use in developing countries, in order to have a vaccine that is effective in children under two years, and which can be incorporated into the infant EPI schedule.
- Field studies in Vietnam of a prototype Vi conjugate vaccine developed by the US NIH found the vaccine to be highly protective in 2-5 year olds for at least four years, when administered in two doses.
- Several newer-generation oral live attenuated typhoid vaccines are also in the pipeline, with the aim of developing highly-immunogenic vaccines that can be given in a single dose.
- None of these newer generation vaccines, including the Vi conjugates, are likely to be licensed and available during the next several years. In the meantime, priority should be given to using the available vaccine tools—Vi and Ty21a.

Typhoid vaccine development is currently going in two main directions:

- a. Vi conjugate vaccines, and
- b. Improved live oral vaccines

Table 5 summarizes information about the most advanced candidates.

A. Vi Conjugate Vaccines

Like many other polysaccharide vaccines, Vi does not induce protective levels of antibodies in children below the age of 2 years nor a booster response. Several research groups are therefore in the process of developing Vi conjugate vaccines, which bind the Vi antigen to a protein, so that it behaves like a T-lymphocyte-dependent vaccine. This should result in a vaccine that is both immunogenic in infants – so it can be included in the infant EPI schedule – and elicits immunological memory if a booster dose is given. Unlike Vi however, the conjugate vaccine will likely require a regimen of at least two doses.

The US NIH developed a prototype Vi conjugate vaccine, using a recombinant exotoxin A of *Pseudomonas aeruginosa* (Vi-rEPA) as a carrier protein. The vaccine was found to be safe and to elicit serum antibody levels in 2-4 year old Vietnamese children that were three times higher than those elicited by Vi in 5-14 year olds [27, 52]. In a Phase III double-randomized placebo-controlled trial among 2-5 year olds in the Mekong Delta of Vietnam, where typhoid is highly-endemic, a 2-dose regimen of the Vi-rEPA vaccine conferred 91% efficacy in preventing blood culture-confirmed typhoid over 27 months of follow-up [27] and 89% after 46 months, suggesting that the vaccine is highly efficacious for at least four years [53]. Analyses of serological responses to a single dose of vaccine in this age group suggested that a single-dose regimen may be adequate.

While the Vi-rEPA vaccine has not been tested for efficacy in infants – the intended targets for the vaccine – a safety/immunogenicity study of the vaccine administered in four doses to 100 infants in Phu Tho, Vietnam, along with other EPI vaccines, has shown no severe adverse reactions.

In order to determine the duration of protection of the vaccine, adults and children injected with one or two doses in the Vietnam trial were followed to measure Vi antibody persistence. After an initial decline during the first six months, the antibody levels reached a plateau and declined more slowly during the next four years. A follow-up study at 10 years after vaccination shows that the antibody levels are still mostly above the predicted protective level. This finding suggests that for people five years and older, the Vi conjugate vaccine does not require re-injection for at least 10 years.

The NIH prototype vaccine is not being developed commercially, but based on these positive results, several organizations and vaccine producers are currently developing Vi conjugate vaccines. These include groups in China, India and Vietnam. They also include the International Vaccine Institute (IVI) and Novartis Vaccines for Global Health, both of whom are collaborating with the US NIH. The goal of both the IVI/NIH and Novartis/NIH programmes is to transfer the technology of the Vi conjugate vaccines to qualified emerging producers, so that low-cost

conjugates can be available for use in developing countries. Instead of using the complex exotoxin A as the protein carrier, all of the above groups are using diphtheria toxoid, which is produced by many developing country producers and is thus readily accessible. The candidate vaccines of these various institutes have been developed in local laboratories and tested in mice. When compared with clinical lots of the NIH construct, all of these candidates have been found to elicit similar serum IgG anti-Vi antibody responses in animals (Shousun Szu, personal communication).

Despite the promising results for the Vi conjugate vaccine candidates, these candidates have a number of uncertainties and caveats. As mentioned above, the efficacy in infants has yet to be determined. The manufacturing process required is considerably more complex than for Vi, and given the likely need for multiple doses, at least for infants, and the greater complexity of production, these vaccines are likely to be more expensive than the current Vi vaccine. A Vi conjugate vaccine is also not likely to be available on the market for at least another five to six years.

Given the uncertainties in the effectiveness of Vi conjugate vaccines in infants, in the timing of their availability and in their costs, countries with a high incidence of typhoid should not wait for Vi conjugate vaccines to become available before considering typhoid vaccination for high-risk populations. This is especially so in view of the availability of Vi and Ty21a vaccines, which are relatively inexpensive, safe, and effective. As shown in Guangxi Province in China, these currently licensed vaccines can make a significant impact in controlling the disease, especially in countries where disease incidence peaks in school-aged children. In hyper-endemic countries, such as Pakistan and India, where incidence is high in pre-school children, Vi conjugate vaccines, incorporated into the infant EPI schedule, will be important tools to control the disease in the future. Vi and Vi conjugates could also be used in a complementary fashion; if boosters are needed later on (*e.g.* during school years) following primary vaccination with a conjugate vaccine, it may be possible to provide Vi as a low-cost booster.

B. Oral Live-Attenuated Typhoid Vaccines

There are at least three oral live attenuated typhoid vaccines in that are currently in stages of clinical development (Table 5). The aim has been to develop a more highly-immunogenic vaccine than Ty21a that would provide protection after a single dose. All of these vaccine candidates are derived from wild-type strain Ty2, as are Ty21a and Vi. All thus far appear to be markedly more immunogenic than Ty21a [3]. One live oral vaccine candidate, CVD 909, has been found to elicit gut-derived antibody secreting cells that secrete IgA anti-Vi antibodies, as well as cell-mediated responses and antibody responses to other antigens. This vaccine, as well as CVD 908-*htrA*, Ty800 (developed by the U.S. firm, AVANT) and ZH9 (developed by Emergent BioSolutions in the U.K.) have undergone safety and immunogenicity trials.

B.1 CVD909 (Centre for Vaccine Development, Baltimore, USA)

Attenuated strain CVD 908-*htrA* which carries deletions in *aroC* and *aroD* (rendering it nutritionally dependent on substrates not available in sufficient concentration in human tissues and in *htrA* (that affects survival in macrophages) was found to be well tolerated and highly immunogenic following ingestion of a single oral dose in placebo-controlled Phase I and II clinical trials. However, a higher level of protection may be attainable if a live, oral vaccine can stimulate immune responses to Vi in addition to the other humoral and cellular responses generated by live oral vaccine like Ty21a. It has been hypothesized that if Vi expression by a live oral vector can be rendered constitutive, so that it is expressed continuously, this might allow the stimulation of serum IgG and mucosal IgA Vi antibodies in orally vaccinated subjects [3]. Accordingly, Wang *et al*, replaced the promoter of *tvfA*, the most upstream gene in the *viaB* locus of strain CVD908-*htrA*, with a strong constitutive promoter to derive strain CVD909, which expresses Vi constitutively [54]. Clinical evaluation of CVD909 in Phase I studies are ongoing.

B.2 Ty800 (AVANT Immunotherapeutics, USA)

Hohmann et al constructed strain Ty800, a *phoP/phoQ* deletion mutant of Ty2 [55]. This strain was generally well tolerated and immunogenic when evaluated in dosage levels from 10^7 to 10^{10} CFU in a small Phase I clinical trial in the U.S. involving 11 subjects [3]. At the highest dosage

level, one of three vaccinees developed diarrhoea. Ty800 stimulated vigorous IgA antibody secreting cell responses and serum O antibody responses. Further clinical evaluation of Ty800 is planned.

B.3 ZH9 (Emergent BioSolutions, UK)

S. typhi strain *S. typhi* (Ty2 *aroC*⁻ *ssaV*⁻) ZH9 contains defined (independently attenuating) deletions in two genes, *aroC* and *ssaV*. The *ssaV* gene is encoded on *Salmonella* Pathogenicity Island 2 (SPI-2). SPI-2 encodes a type III secretion system and *ssaV* is a structural gene encoding part of the secretion apparatus. SPI-2 mutations are attenuating in mice, and there is evidence that this is because SPI-2 is required for survival and growth within macrophages, which normally mediate the systemic spread of the organism. The rationale for inclusion of the *ssaV* deletion mutation is that it will prevent systemic spread of the vaccine strain in humans, and therefore prevent bacteraemias. *aro* mutations are well described as being attenuating for *Salmonella* in humans.

To date *S. typhi* (Ty2 *aroC*⁻ *ssaV*⁻) ZH9 has been administered to over 100 healthy adult volunteers in four studies. In the first study 9 subjects (3 per cohort) received doses of either, 10⁷, 10⁸ or 10⁹ CFU of a frozen formulation of the vaccine. In the second study 48 subjects (16 per cohort) received doses of 5 x 10⁷, 5 x 10⁸ or 5 x 10⁹ CFU of a freeze-dried formulation of the *S. typhi* (Ty2 *aroC*⁻ *ssaV*⁻) ZH9 vaccine. In the third study 32 subjects received one dose of 5 x 10⁹ CFU of the freeze-dried formulation and in the fourth study, conducted in Vietnam, 16 subjects received one dose of 5 x 10⁹ CFU of the freeze-dried formulation. These studies indicate that the vaccine is immunogenic with a good safety profile. A Phase II study in over 100 Vietnamese children between 5 and 14 years of age has recently been completed [67, 68].

Table 5. Comparative Properties of Four Newer Generation Typhoid Vaccines Currently Under Development				
Property/Feature	Vi-DT conjugate (NIH and partners)*	CVD909 (CVD / Acambis / Crucell)	Ty800 (Avant)	ZH09 (Emergent)
Type of vaccine	Subunit vaccine (Vi polysaccharide conjugated to a protein carrier)	Live attenuated	Live attenuated	Live attenuated
Delivery route	Injectable	Oral	Oral	Oral
Projected target age groups	All ages	All ages	All ages	All ages
Number of doses	Undetermined Target: one dose for persons over 2 years of age; and two doses for infants	Undetermined Target: one dose	Undetermined Target: one dose	Undetermined Target: one dose
Stage of development and testing	Phase IIb trial of efficacy completed in Vietnam for prototype Vi-rEPA. Vi-DT vaccine in animal testing. Technology to be transferred to developing country producers.	Phase II studies	Phase II studies	Phase II trials completed in industrialized and developing countries
Safety and immunogenicity	High in industrialized and endemic populations	High in industrialized countries No data for endemic populations	High in industrialized countries No data for endemic populations	High in industrialized and endemic countries
Safety in HIV+ persons	Presumed safe	Uncertain	Uncertain	Uncertain
Efficacy in endemic	91% in 2-5 year olds No data on efficacy in	No data	No data	No data

Property/Feature	Vi-DT conjugate (NIH and partners)*	CVD909 (CVD / Acambis / Crucell)	Ty800 (Avant)	ZH09 (Emergent)
populations	infants			
Duration of protection	At least 46 months	No data	No data	No data
Correlates of protection	Exists	Does not exist	Does not exist	Does not exist
Time to market and licensing pathway	5-6 years It is possible that the vaccine can be licensed based on immunogenicity alone	8-10 years Efficacy trial in ~6,000 - 10,000 individuals needed (in high incidence area)	8-10 years Efficacy trial in ~6,000 - 10,000 individuals needed (in high incidence area)	4-5 years from licensure Efficacy trial in ~6,000 - 10,000 individuals needed (in high incidence area)
Potential incorporation into EPI schedule	Easily integrated with existing EPI schedules	Potentially (No data)	Potentially (No data)	Potentially (No data)
Feasibility of technology transfer to local producers	Feasible. Several producers manufacture Vi and have track record in developing other conjugates	Feasible	Feasible	Feasible
* Sources: Szu 1987, Szu 1989, Szu 1991, Kossaczka 1999, Lin 2001, Mai 2003				

VI. Suggested Recommendations

1. In view of the continued high incidence of typhoid fever and increasing antibiotic resistance, and given the safety, efficacy, feasibility and affordability of two licensed vaccines (Vi and Ty21a), countries should consider the programmatic use of typhoid vaccines for controlling endemic disease;
2. In most countries, the control of the disease will require only vaccination targeted to high-risk groups and populations, as opposed to universal vaccination;
3. The selection of populations and age groups to target and the delivery strategy (school- or community-based vaccination) should be up to specific countries and will depend on the local context (*eg.* age pattern of the disease, school enrolment rates, *etc.*);
4. The selection of typhoid vaccine – Ty21a and Vi – should be made by the countries themselves, and depend on the capacity of the local EPI programme and other logistic and cultural factors, and utilizing opportunities coupled to other public health interventions in these specific age groups;
5. The availability of licensed typhoid vaccines for the poor will be enhanced by the pre-qualification by WHO of these products and by the enhanced global awareness and commitment to reduce typhoid disease burden;
6. Due to the epidemic potential of typhoid, and past observations in the effectiveness of vaccination in interrupting outbreaks, typhoid vaccination is recommended for outbreak control;
7. All typhoid vaccination programmes should be implemented in the context of other efforts to control the disease, including health education, water quality and sanitation improvements, and training of health professionals in diagnosis and treatment;

8. Given the importance of information on disease incidence for targeting vaccination and assessing impact, priority should be given to strengthening surveillance systems for typhoid fever, including sentinel site surveillance in pre-school (2-4 year olds) and school-aged children (5-15 year olds). The development of reliable and appropriate diagnostics assays for developing countries is required;
9. Development and research of new typhoid vaccines (such as the Vi conjugate vaccine) are encouraged for use in infants and young children, but this should not limit the implementation of the current available vaccines for control of endemic disease.

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Appendix:

Spreadsheet with estimates for demand for typhoid vaccination in 30 high-risk countries

Region*	Country**	Percent Urban**	Total Population***	Population 5-9 years***	Population 10-14 years***	Population 5-14 years	3-yearly dose^	
							50% Coverage	80% Coverage
Southern Africa								
	1 Botswana	53.2	1,579,000	109,000	117,000	226,000	72,139	108,209
	2 Lesotho	17.8	1,858,000	186,000	193,000	379,000	40,477	60,716
	3 Namibia	32.4	1,897,000	261,000	258,000	519,000	100,894	151,340
	4 South Africa	56.9	42,716,000	2,675,000	2,798,000	5,473,000	1,868,482	2,802,723
	5 Swaziland	23.3	1,150,000	117,000	120,000	237,000	33,133	49,699
South-central Asia								
	1 Afghanistan	21.3	27,756,000	5,584,000	5,230,000	10,814,000	1,382,029	2,073,044
	2 Bangladesh	23.2	135,657,000	20,251,000	20,121,000	40,372,000	5,619,782	8,429,674
	3 Bhutan	9.6	2,094,000	374,000	351,000	725,000	41,760	62,640
	4 India	27.7	1,034,173,000	111,398,000	111,155,000	222,553,000	36,988,309	55,482,463
	5 Iran (Islamic Republic of)	64.2	67,538,000	6,242,000	6,307,000	12,549,000	4,833,875	7,250,812
	6 Kazakhstan	56.3	16,742,000	1,562,000	1,682,000	3,244,000	1,095,823	1,643,735
	7 Kyrgyzstan	35.4	4,822,000	659,000	654,000	1,313,000	278,881	418,322
	8 Maldives	27.5	320,000	65,000	62,000	127,000	20,955	31,433
	9 Nepal	13.4	25,874,000	4,132,000	4,084,000	8,216,000	660,566	990,850
	10 Pakistan	33.1	147,663,000	19,316,000	19,241,000	38,557,000	7,657,420	11,486,130
	11 Sri Lanka	15.7	19,577,000	1,430,000	1,482,000	2,912,000	274,310	411,466
	12 Tajikistan	25.9	6,720,000	1,249,000	1,187,000	2,436,000	378,554	567,832
	13 Turkmenistan	45.1	4,689,000	719,000	691,000	1,410,000	381,546	572,319
	14 Uzbekistan	37.3	25,563,000	3,492,000	3,531,000	7,023,000	1,571,747	2,357,621
South-eastern Asia								
	1 Brunei Darussalam	71.1	351,000	38,000	37,000	75,000	31,995	47,993
	2 Cambodia	16.9	12,890,000	2,067,000	1,927,000	3,994,000	404,992	607,487
	3 Indonesia	42	231,326,000	22,242,000	22,911,000	45,153,000	11,378,556	17,067,834
	4 Lao People's Dem. Republic	18.9	5,778,000	1,091,000	1,053,000	2,144,000	243,130	364,694
	5 Malaysia	61.8	22,662,000	3,051,000	2,908,000	5,959,000	2,209,597	3,314,396
	6 Myanmar	28	42,282,000	3,120,000	3,290,000	6,410,000	1,076,880	1,615,320
	7 Philippines	58.5	82,995,000	10,912,000	10,788,000	21,700,000	7,616,700	11,425,050
	8 Singapore	100	4,453,000	435,000	415,000	850,000	510,000	765,000
	9 Thailand	31.1	63,645,000	4,420,000	4,600,000	9,020,000	1,683,132	2,524,698
	10 Timor-Leste	24.5	953,000	148,000	145,000	293,000	43,071	64,607
	11 Viet Nam	24.3	80,577,000	7,972,000	8,091,000	16,063,000	2,341,985	3,512,978
TOTAL			2,116,300,000	235,317,000	235,429,000	470,746,000	90,840,722	136,261,083

* Region included in this table are based on high incidence regions described in the Global Burden of Typhoid Fever by Crump et al.

** Source: United Nations Department of Economic and Social Affairs, Population Division; 2000 data

*** Source: US Census Bureau, Global Population Profile 2002

^ Vaccine dose requirement includes 10% wastage of the vaccine